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(54) Pharmaceutical compositions containing procaine

(57) Pharmaceutical compositions containing procaine are used in improving the condition of skin and/or mucosa, especially gastro-intestinal mucosa.

Application of procaine to skin and/or mucosa can improve the condition thereof in a number of ways including increasing its resistance to non-mechanical injury and to degeneration and increasing regeneration as for example in wound healing and skin graft taking. The compositions are also useful in combatting hair-loss.

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SPECIFICATION

Biologically Active Substances

The present invention relates to the improvement of skin condition.

Although there is an extensive range of products available in the cosmetic market which allegedly improve skin condition these generally comprise merely barrier and/or moisturising creams which do little more than attempt to control oil and/or water balance in the skin either by creating a barrier to transfer across the skin or by attempting to restore excessive loss from the skin. Thus such products do little if anything to improve the functioning of the skin—especially in relation to resistance to and/or recovery from injury and/or degeneration.

It is an object of the present invention to avoid or minimise one or more of the above disadvantages.

The present invention provides procaine for use in improving the condition of skin and/or mucosa, especially gastro-intestinal mucosa.

In accordance with the present invention the application of procaine to skin and/or mucosa has been found to improve condition in a number of ways including improved healing of wounds and ulcers (both internally and externally—varicose ulcers on the one hand and peptic ulcers on the other hand), and protection against non-mechanical injury e.g. from injurious chemical materials, and against degeneration from other causes including ageing. The improved condition can also include maintenance of vitality and improved skin graft taking in the case of both attached or free and partial or full thickness grafts. Furthermore procaine has been found to block vagal nerve impulses, inhibit vagal secretory patterns and suppress gastric acid secretion thereby further enhancing the improvement of gastro-intestinal mucosa condition reducing stress ulceration.

In at least some types of premature hair loss application of procaine to the scalp has moreover been found to reduce or arrest hair loss and/or stimulate new hair growth from hair follicles whose function had previously been impaired but are not yet dead.

Other beneficial effects that can contribute to the above-mentioned beneficial actions of procaine are its antispasmodic effects on smooth muscle and analgesic effects in relation to organic or visceral abdominal pain via blockade of neurologic transmission of impulses.

Advantageously the procaine is used in combination with a xanthine, preferably one selected from theophylline, theobromine, aminophylline, ephidrine, and caffeine, most preferably caffeine. In this case there is obtained an enhanced activity whereby the skin condition is further improved to the extent that dermatitis and allergic conditions can be arrested and even reduced.

Advantageously there is also included a vasodilator such as for example menthol in order to further increase the effectiveness of the procaine in the skin.

Advantageously also there may be included an anti-ischaemic substance and in particular papaverine, and/or an anti-cholinergic and/or vagal nerve blocking substance, especially one or more compounds selected from propoxycaine and amethocaine.

In a further aspect the present invention provides procaine and procaine with caffeine in intimate admixture with a physiologically acceptable carrier therefor for use in improving the condition of skin and/or mucosa.

In another aspect the present invention provides a topical formulation comprising procaine or procaine with caffeine in intimate admixture with a pharmaceutically acceptable vehicle therefor. The vehicle should be 'acceptable' in the sense of being generally non-deleterious to the skin of the subject being treated and compatible with the other ingredients of the formulation. It will of course be appreciated that certain individuals have significantly more sensitive skins than the average and that in these special cases alternative vehicles to those normally used may need to be tried.

Suitable vehicles are well known in the art being noted for example in such standard works as the British Pharmacopoeia and the British National Formulary and include ointment bases and cream bases as well as lotions, pastes, jellies, sprays, aerosols and bath oils. Ointments and creams may contain oleaginous absorption colloidal clays, thickening agents such as gum tragacanth or sodium alginate and other pharmaceutically acceptable accessory ingredients such as humectants, preservatives, buffers and antioxidants which have utility in such formulations.

In general cream formulations are preferred as being most acceptable to the majority of users. A particularly convenient base is one utilizing cetomacrogol, comprising for example 30% w/v cetomacrogol emulsifying ointment (30% w/v cetomacrogol emulsifying wax, 20% w/v liquid paraffin wax, 50% white soft paraffin) in freshly boiled and cooled purified water with for example 0.1% w/v chlorocresol or 0.08% w/v propyl hydroxybenzoate, 0.15% w/v methyl hydroxybenzoate and, 1.5% w/v benzyl alcohol.

In general the topical formulations of the invention contain at least 0.5% w/w of procaine, preferably from 1 to 30% w/w, and most preferably from 2 to 10% e.g. 5% w/w of procaine. Where caffeine is included this is generally used in an amount of from 1 to 30% w/w.

In addition procaine (optionally with other active ingredients and/or a suitable vehicle) can be administered orally or parenterally, in particular by intramuscular injection.

For oral administration the procaine and any accompanying material may be presented as a draught in water or in a syrup, in capsules, cachets, boluses or tablets, as an aqueous or oleaginous solution or suspension or in suspension in a syrup, such suspensions optionally including suspending agents or as an oil-in-water or water-in-oil emulsion. Where desirable or necessary flavouring, sweetening, preserving, thickening or emulsifying agents may be included in the formulation. Tablets

may contain the procaine and any accompanying material as a powder or granules optionally mixed with binders, lubricants, inert diluents or surface-active or dispersing agents.

For parenteral administration the procaine and any accompanying material may be presented in sterile solutions or suspensions in aqueous or oleaginous vehicles, which may also contain preservatives and material for rendering the solution or suspension isotonic with the blood of the intended recipient. Such formulations may conveniently be presented in unit-dose or multi-dose sealed containers.

For administration orally in liquid form or parenterally the procaine is preferably presented in solution or suspension or emulsion at a concentration of from 0.5 to 15% more preferably 2 to 5% w/v in unit multi-dose form. When presented in unit-dose form each unit dose preferably contains from 50 to 500 mg of procaine.

In general for the purposes of treating gastro-intestinal mucosa the procaine is administered at a dosage rate of from 35 to 140 mg/kg of subject bodyweight per day, preferably from 60 to 80 mg/kg/day. The dosage may be administered in one or more doses per day and preferably is administered at intervals of from 2 to 6 hours, most preferably every 4 hours. Advantageously the procaine is administered in a slow release or sustained release vehicle, various suitable vehicles of this type being known in the art.

Where papaverine is included this is generally used at a dosage rate of the order of 1 mg/kg/day.

The present invention also provides a process for producing a pharmaceutical formulation of the invention comprising bringing into intimate association a procaine or procaine with caffeine and a pharmaceutically acceptable vehicle therefor.

Procaine, optionally with caffeine and, if desired, menthol also, may be administered to human beings to improve skin condition and the present invention accordingly extends to a method of improving the condition of skin or mucosa comprising administration of procaine (optionally with one or more of caffeine and menthol) to the skin or mucosa of a subject.

Where skin is being treated the procaine will normally be applied in the form of a topical formulation of the invention at least once a day, preferably 2 or 3 times a day. The formulation is generally spread over the area to be treated and gently rubbed in.

Where mucosa are being treated, especially the gastro-intestinal mucosa, the caffeine is preferably omitted.

In practice procaine is normally used in the form of an acid addition salt. Any physiologically acceptable acid addition salt may be used in accordance with the present invention and accordingly any references herein to procaine are to be understood as extending to such acid addition salts unless the contrary is indicated. A particularly suitable acid addition salt that may be mentioned is procaine hydrochloride and in the following examples references to procaine are to be understood as referring to procaine hydrochloride unless the contrary is indicated.

Further preferred features and advantages of the invention will appear from the following detailed examples given by way of illustration only.

EXAMPLE 1

Preparation of Cream for Treating Skin

A topical cream having the following composition was prepared by the method described hereinbelow.

Procaine hydrochloride (anhydrous)	5g
Caffeine hydrate	2g
Menthol crystals	1g
Cetomacrogol 'A' (B.P.)	add to 100g

The formula is prepared in a medium of 25°C temperature. 5g procaine hydrochloride is mixed with 2g of caffeine in a glass or stainless steel container and 92g cetomacrogol 'A' is added and mixed for 10 minutes. After standing for 30 minutes 1g of menthol crystals finely ground is added and mixed for 10 minutes. The resulting mixture is placed into an airtight opaque glass container and stored at a temperature not exceeding 26°C. No direct light should be projected at the container during the preparation which was carried out at approximately 25°C. After preparation the formula should not be used for at least 12 hours, should not be left exposed to the air for long periods, and should not be directly exposed to the sun.

EXAMPLE 2

Cream for Treating Skin

A topical cream similar to that of Example 1 was prepared using a similar procedure but omitting the menthol crystals.

EXAMPLE 3

Cream for Treating Skin

A topical cream similar to that of Example 1 was prepared using a similar procedure but omitting both the caffeine hydrate and the menthol crystals.

EXAMPLE 4

Use of Procaine Cream

In a double blind clinical trial the effect of a once daily topical application of a 5% procaine alone hydrochloride cream (similar to that of Example 3) for four weeks on hyperkeratosis of face and limb skin in the elderly subject was investigated so as to assess the effect of procaine. There were 19 male and female subjects with an average age of 59 years and 11 male and female controls with an average age of 53 years. Procaine was significantly better than placebo in that it caused in 14 patients complete exfoliation of the hyperkeratotic lesions and replacement by healthy soft skin, and in the remaining 5 patients an incomplete exfoliation of their lesions at the end of the 4 week experimental period. Placebo had no effect on controls. This trial demonstrated a remarkable improvement of skin condition by procaine.

EXAMPLE 5

Use of Procaine With Caffeine Cream

To investigate the effect of caffeine on the effectiveness of procaine a similar double blind trial to that of Example 4 was conducted for 4 weeks on 12 treatment subjects (average age 61 yrs) and 9 controls (average age 56 yrs) using a daily topical application of a cream containing 5% procaine hydrochloride with 2% caffeine (similar to that of Example 2) on hyperkeratotic lesions on face and limbs.

At the end of the 4 week treatment course all the subjects had completely replaced lesions by normal skin. It is concluded that administration of caffeine with procaine enhances the rejuvenating effect of procaine on the skin.

EXAMPLE 6

Use of Procaine and Caffeine Cream

The protective effect of 5% procaine hydrochloride and 2% caffeine (similar to that of Example 2) topically applied against ultraviolet rays was investigated in 11 patients (average age 19 yrs). All patients had a previous history of skin irritation following exposure to the sun. Application of an overnight treatment commencing on the night before exposure and on successive nights during the period of exposure to the sun, completely protected the skin in all subjects against the previously experienced sun-induced irritation. Thus, a combination of caffeine with procaine protected subjects against sun rays (ultraviolet radiation) induced irritation and injury.

EXAMPLES 7—9

Activity of Procaine Solution on Gastric Mucosa

EXAMPLE 7

In the pylorus-ligated rat, the vagally mediated maximum gastric acid secretion stimulation was completely blocked by orogastric intubation of one ml of a 10% w/v aqueous procaine hydrochloride solution.

EXAMPLE 8

Similarly, procaine hydrochloride in a dose of one ml of a 10% w/v aqueous solution completely blocked reserpine induced (reserpine administered subcutaneously at a dosage rate of 0.2 mg/kg bodyweight) vagally mediated gastrin and histamine release and stimulation of gastric acid secretion in Sprague-Dawley rat. These tests indicated the activity of procaine as a medical vagotomy agent.

EXAMPLE 9

In Sprague-Dawley rats a twice daily oral administration of one ml of procaine hydrochloride 5% w/v significantly enhanced the healing of aspirin 200 mg/kg bodyweight and reserpine 5 mg/kg bodyweight induced acute gastric mucosal injury ($p<0.01$).

EXAMPLE 10

Use of Procaine in Treatment of Gastric Mucosa

In a double blind clinical trial, one capsule containing 1g. procaine hydrochloride crystals or placebo was administered orally once every 6 hours to a group of patients with symptomatic and endoscopically confirmed duodenal ulceration. The procaine receiving group comprised 21 subjects (all males and of an average age 32 yrs) and the control group comprised 10 male subjects of an average age 27 years. Both groups had no previous history of peptic ulceration and were of a present history of less than 10 days.

The procaine treatment completely controlled all ulcer symptoms in all subjects within 24 hours and all subjects were allowed their normal original meals without any restrictions 3 days after commencing treatment without any observed digestive discomfort. After six weeks of treatment, 18 subjects were found to be completely healed upon endoscopic examination.

The placebo group did not experience any beneficial effects in relation to their symptoms and were intolerant of their original meals when re-instituted after 3 days of commencement of the treatment. These comprised milk, biscuits, fruit and fresh or boiled vegetables taken as small meals six times a day (similar to the procaine group). After six weeks of treatment five subjects only had endescopically healed ulcers.

EXAMPLE 11

Preparation of Capsule for Oral Administration

The following composition was prepared in a glass container screened off from any direct light and at a room temperature of 26°C by mixing the powders in the proportions indicated and then filling gelatinous capsules with the mixture at a rate of 500 mg per capsule. These were then stored in opaque containers away from direct light and at a room temperature of 26°C. All capsules were used within six months of preparation.

Contents of each capsule:

Procaine hydrochloride	500 mg
Amethocaine hydrochloride	30 mg
Propopoxycaine hydrochloride	30 mg

EXAMPLE 12

Use of Capsules in Treatment of Gastric Mucosa

In 10 male subjects of an age range 24—31 yrs with classic symptoms of duodenal ulceration for less than a week and no ulceration but rather duodenitis on endoscopy, administration of 2 capsules (of Example 11) six hourly intervals completely controlled all symptoms immediately and all patients remained symptom-free and on normal diet for the six week treatment where endoscopy at the end of this period demonstrated no duodenal abnormality.

In connection with Examples 11 and 12 it should be noted that it has now been found that the use of either or both of amethocaine and propoxycaine together with procaine provides a significant extension of the duration of activity of procaine as compared with procaine when used alone. Accordingly in a further aspect the present invention provides procaine in intimate admixture with at

least one of propoxycaine and amethocaine, especially for use in the treatment of gastric mucosa, as well as pharmaceutical compositions thereof with a pharmaceutically acceptable carrier therefor.

In addition to the above-demonstrated beneficial effects in the treatment of duodenal ulceration, the compositions of the invention have also been found to control the symptoms of gastroduodenal dysfunction (e.g. indigestion) and acute and chronic ulceration as well as healing of chronic gastric ulceration.

EXAMPLE 13

Acute Toxicity Studies

To investigate the acute toxicity effects of the formula in multiples of its therapeutic doses in a variety of animal species it was prepared by dissolving 5g of procaine hydrochloride (anhydrous) in 100 ml double distilled water then adding 2g caffeine hydrate and 1g menthol crystals. A colourless transparent solution was obtained. A double and triple concentrations were similarly prepared.

Six groups of ten male and female Sprague-Dawley rats weighing between 150—250 g were denied solid food for 24 hours before study. Under light ether anaesthesia and by orogastric intubation with a 6 FG tube, one ml of each of the concentrations was instilled into a group. Similarly, one ml of each of the concentrations was intraperitoneally injected into a group.

Groups were then observed for 24 hours for mortality, drowsiness, withdrawal, depression, excitation, vomiting or diarrhoea, then allowed food and similarly observed for another week. No mortality was associated with administration of the formula in the concentrations mentioned and there were no observed adverse effects in any case.

The same formula concentrations were freshly prepared and the same procedure repeated using groups of ten male and female Guinea-pigs. The safety of formula and its freedom from adverse side effects was reproduced in this species as well.

It was concluded that the formula is safe for topical uses in man.

EXAMPLE 14

Clinical Trials

All trials were conducted by the double blind method on the composition of Example 1 against its base.

1. Twelve females of an age range (34—47 years) complaining of itching of the skin covering the medial side of the lower third of the leg and associated with incompetent medical venous perforators, were treated for four weeks with twice daily application of the formula with elastic stockings. Six other females (age 41—45 years) of a similar complaint and condition were treated with twice daily application of the base with elastic stockings. Within 48 hours all treatment subjects obtained complete relief whereas two patients in the control group had similar relief within the same period.

2. A group of males (n=20, age 20—34 years) were instituted on a twice daily application of the formula immediately following repair of their indirect inguinal hernias to investigate protection against post-operative hyperaesthesia. The control group (20 males, age 23—29 years) received a similar treatment using the formula base. All operations were performed by the same surgeon and treatment was continued for two weeks. The formula significantly relieved local discomfort and pain relative to treatment with its base. In all the treatment cases the wound was not sensitive to touching and particularly so during removal of stitches. In the control group, all patients were extremely sensitive to wound touching till the end of their second post-operative week.

3. A group of 37 females (age range 45—57 years) with signs of housewife dermatitis (dry, rough and fissured skin) of the fingers was instituted on a twice daily application of the formula for 12 weeks. Another group of 16 females (age 41—47 years) with a similar condition was instituted on twice daily treatment with the formula's base for 12 weeks. Both groups were instructed to avoid domestic housework without wearing rubber gloves.

After six weeks, 20 females in the treatment group were completely satisfied with their treatment and demonstrated smooth non-fissured fingers. In the control group there were two similar cases. At the end of the treatment course, 28 females in the treatment group were completely satisfied with their treatment and had fingers with smooth non-fissured skin whereas only 4 females in the control group demonstrated similar results.

Both groups were then instituted on a once daily application of their treatment for another 12 weeks with the precaution of wearing rubber gloves during housework. At the end of the six months of treatment, all patients were completely satisfied with their treatment and demonstrated smooth non-fissured fingers. Upon follow-up for six months, there were no relapses among the group and their dermatitis remained in control. Females in the control group had no change in their response during the second three months relative to results in the first three months of treatment.

CLAIMS

1. An agent comprising procaine and/or a physiologically acceptable acid addition salt thereof for use in improving the skin and/or mucosa.

2. An agent as claimed in claim 1 wherein said agent includes at least one of amethocaine and propoxycaine.

3. An agent as claimed in claim 1 or claim 2 which includes a xanthine.

4. An agent as claimed in claim 3 wherein said xanthine is selected from theophylline, theobromine, aminophylline, ephidrine, and caffeine.

5. An agent as claimed in any one of claims 1 to 4 which includes a vasodilator.

6. An agent as claimed in claim 5 wherein said vasodilator comprises menthol.

7. An agent as claimed in any one of claims 1 to 6 which includes at least one of an anti-ischaemic substance, an anti-cholingeric substance, and a vagal nerve blocking substance.

8. An agent as claimed in claim 7 which includes at least one papaverine, propoxycaine, and amethocaine.

9. An agent as claimed in any one of claims 1 to 8 which includes castor oil.

10. An agent for use in improving the condition of skin and/or mucosa substantially as described hereinbefore with particular reference to any one of Examples 1 to 14.

11. A cosmetic composition suitable for use in improving skin condition comprising a combination as claimed in any one of the preceding claims in intimate admixture with a physiologically acceptable carrier therefor.

12. A composition as claimed in claim 11 which is in the form of a topical formulation.

13. A method of improving the skin condition of a human subject comprising the topical application to the skin of said subject of a composition as claimed in claim 12.

14. A method as claimed in claim 13 wherein said application is repeated several times over a period of several days.

15. A method of improving the skin condition of a human subject comprising the topical application to the skin of said subject of a composition substantially as described hereinbefore with particular reference to any one of Examples 4 to 6 and 14.

16. An agent as claimed in any one of claims 1 to 10 for use in the preparation of a medicament for use in improving the skin and/or mucosa.

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